

# Treatment approach and outcomes of patients with accelerated/blast-phase myeloproliferative neoplasms in the current era

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## Key Points

- Median OS in MPN-AP/BP is 0.86 years in a modern cohort without significant difference based on frontline treatment choice.
- Median OS in those that underwent allo-HSCT is 2.3 years from time of allo-HSCT; response before allo-HSCT did not affect survival.

Progression of myeloproliferative neoplasms (MPNs) to accelerated or blast phase is associated with poor survival outcomes. Since 2017 there have been several therapies approved for use in acute myeloid leukemia (AML); these therapies have been incorporated into the management of accelerated/blast-phase MPNs (MPN-AP/BP). We performed a multicenter analysis to investigate outcomes of patients diagnosed with MPN-AP/BP in 2017 or later. In total, 202 patients were identified; median overall survival (OS) was 0.86 years. We also analyzed patients based on first-line treatment; the 3 most common approaches were intensive chemotherapy (n = 65), DNA methyltransferase inhibitor (DNMTi)-based regimens (n = 65), and DNMTi + venetoclax-based regimens (n = 54). Median OS was not significantly different by treatment type. In addition, we evaluated response by 2017 European LeukemiaNet AML criteria and 2012 MPN-BP criteria in an effort to understand the association of response with survival outcomes. We also analyzed outcomes in 65 patients that received allogeneic hematopoietic stem cell transplant (allo-HSCT); median OS was 2.30 years from time of allo-HSCT. Our study demonstrates that survival among patients with MPN-AP/BP is limited in the absence of allo-HSCT even in the current era of therapeutics and underscores the urgent need for new agents and approaches.

## Introduction

Philadelphia-chromosome-negative myeloproliferative neoplasms (MPNs) are a heterogeneous group of hematopoietic stem cell disorders characterized by proliferation of myeloid cells, activation of the JAK/STAT pathway, and a variable risk of progression to accelerated phase (AP) or blast phase (BP)

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The full-text version of this article contains a data supplement.

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that is influenced by disease phenotype and clinical, cytogenetic, and molecular features.<sup>1-3</sup> AP is defined as 10% to 19% blasts in the peripheral blood or bone marrow whereas BP requires  $\geq 20\%$  blasts.<sup>4</sup> Although the median overall survival (OS) of patients with chronic-phase MPN is several years, development of an AP/BP MPN (MPN-AP/BP) is associated with limited OS, particularly in the absence of allogeneic hematopoietic stem cell transplant (allo-HSCT). The median OS for patients with MPN-AP ranges from 12 to 18 months<sup>5-7</sup> whereas the median OS of those with MPN-BP is 3 to 5 months.<sup>8-11</sup>

Since 2017, there have been several novel therapies approved for use in acute myeloid leukemia (AML) that have led to significant evolution in the treatment approach in this disease.<sup>12,13</sup> These treatment approaches are often applied to patients with MPN-AP/BP despite being molecularly and morphologically distinct from de novo AML.<sup>14-18</sup> There are limited prospective data for the use of these therapies in MPN-AP/BP, and primarily real-world data have been analyzed to characterize their efficacy. There has been a particular focus on the outcomes of patients treated with venetoclax (VEN)-based therapies and isocitrate dehydrogenase (IDH) inhibitors. Median OS with VEN-based regimens ranges from 4 to 8 months<sup>19-22</sup> while utilization of IDH inhibition has demonstrated median OS ranging from 10 to 15 months.<sup>23-25</sup> In addition, prospective efforts have investigated the use of DNA methyltransferase inhibitors (DNMTi's) in combination with the JAK inhibitor ruxolitinib with reported median OS ranging from 7 to 9.5 months.<sup>26,27</sup>

Given the limited prospective data for therapies in MPN-AP/BP, there is heterogeneity and lack of consensus regarding treatment approach in the current era of myeloid therapies. Therefore, we aimed to analyze outcomes in adult patients with MPN-AP/BP diagnosed in 2017 or later using a large multicenter retrospective cohort to better understand the impact of treatment approach. We also investigated assessment of response by both AML-specific and MPN-BP specific criteria in relation to survival outcomes. In addition, we analyzed outcomes in the patients that underwent allo-HSCT for MPN-AP/BP.

## Methods

All adult patients with MPN-AP/BP diagnosed in 2017 or later were identified at 9 participating academic centers. MPN-AP/BP was defined as the development of  $\geq 10\%$  blasts in the peripheral blood or bone marrow in patients with an underlying MPN. All participating centers obtained approval from their institutional review board. Patient demographics were collected including age at diagnosis, sex and self-reported race/ethnicity; 1 participating center was unable to contribute race/ethnicity data. Disease characteristics and treatment approaches for both chronic-phase MPN and MPN-AP/BP were collected. For patients with cytogenetic/molecular data available at the time of MPN-AP/BP diagnosis, a prognostic risk score was assigned using 2017 European LeukemiaNet (ELN) AML criteria.<sup>28</sup> Response to therapies administered for treatment of MPN-AP/BP were assessed using both 2017 ELN AML response criteria and 2012 MPN-BP response criteria.<sup>28,29</sup> Of note, 1 participating center was only able to characterize response using 2017 ELN criteria. All analyses were performed using SAS software version 9.4 (Cary, NC).

Each institution received approval from the institutional review board to conduct this retrospective project.

## Results

### Patient demographics and molecular information

In total, 202 patients with MPN-AP/BP diagnosed during the specified period were identified; 140 patients had MPN-BP at time of progression whereas 62 had MPN-AP. The median age at time of MPN-AP/BP diagnosis was 68.6 years (range, 21-91) and 39.6% were women. The most common chronic-phase MPN in patients was primary myelofibrosis, which was noted in 33% of patients. When looking at underlying driver mutations at time of chronic-phase MPN, 61% of patients had *JAK2*-mutated disease, 16% had *CALR*-mutated disease, 9% had *MPL*-mutated disease, and 13% of patients had "triple-negative" disease. The most common therapies directed at chronic-phase MPN were hydroxyurea in 61% of patients and JAK inhibitor therapy in 36% of patients; 6 patients had previously undergone allo-HSCT for their chronic-phase MPN. Additional characteristics are summarized in [Table 1](#).

Median laboratory values at time of MPN-AP/BP diagnosis are characterized in [Table 1](#). Of 189 patients with available data needed for 2017 ELN AML risk stratification, 67% had high-risk disease. In addition, 166 patients had next-generation sequencing performed at time of MPN-AP/BP diagnosis. Mutations with an incidence of  $\geq 10\%$  included *ASXL* (31%), *TP53* (26%), *SRSF2* (23%), *TET2* (20%), *RUNX1* (17%), *IDH2* (14%), *DNMT3A* (11%), and *CBL* (10%). In addition, 7% and 4% of patients had disease with an *IDH1* mutation and a *FLT3* mutation, respectively.

### Survival outcomes and response to therapy

The median OS for the entire 202 patient cohort was 0.86 years ([Figure 1A](#)); median OS for patients diagnosed with MPN-AP was 1.09 years whereas it was 0.67 years for those diagnosed with MPN-BP. Median follow-up time was 0.75 years; 51 patients were alive at time of data analysis. We also analyzed outcomes and responses based on the treatment approach for MPN-AP/BP. Of note, 1 patient proceeded directly to allo-HSCT and 7 patients received supportive care alone. Sixty-five patients (32%) received intensive chemotherapy (IC) as their initial therapy, 65 patients (32%) received DNMTi-based therapy, 54 patients (27%) received DNMTi + VEN-based therapy, 4 patients received a targeted inhibitor as monotherapy, and 6 patients received other therapies. The specific therapies are summarized in supplemental [Table 1](#). Twenty-seven patients were treated in the context of a clinical trial. We analyzed differences in patient and disease characteristics among those treated with IC, DNMTi-based therapy, and DNMTi + VEN-based therapy ([Table 2](#)); patients treated with IC were significantly younger ( $P < .0001$ ) whereas patients treated with DNMTi-based therapy had significantly lower marrow and peripheral blood blasts ( $P = .009$  and  $P = .0006$ , respectively). Using Kaplan-Meier analysis, estimated OS based on treatment approach was also analyzed. Median OS for the IC group was 0.68 years, for the DNMTi + VEN-based group was 0.71 years, and 1.25 years for the DNMTi-based group ( $P = .47$ ; [Figure 1B](#)). Of note, the median OS of the DNMTi-based group was not significantly different when compared with those treated with IC or DNMTi + VEN-based approaches ( $n = 119$ ; median OS, 0.72 years;  $P = .80$ ).

**Table 1. Patient demographics and disease characteristics during chronic-phase MPN and at diagnosis of MPN-AP/BP**

Demographics	N = 202
Age (y) at chronic-phase MPN diagnosis, median (range)	61.9 (21.9-91.0)
Female, n (%)	80 (39.6)
<b>Race/ethnicity, n (%)</b>	<b>n = 158</b>
White	142 (89.9)
Black	9 (5.7)
Asian	3 (1.9)
Other	4 (2.5)
Hispanic ethnicity	11 (7.0)
<b>Chronic-phase MPN</b>	<b>N = 202</b>
Polycythemia vera	40 (20%)
Essential thrombocythemia	57 (28%)
Primary myelofibrosis	67 (33%)
MPN-not otherwise specified/other	38 (19%)
<b>Driver mutation</b>	<b>N = 202</b>
JAK2	124 (61%)
CALR	33 (16%)
MPL	18 (9%)
Triple-negative	27 (13%)
<b>Therapies received for chronic-phase MPN</b>	<b>N = 202</b>
Hydroxyurea	124 (61%)
JAK inhibitor	72 (36%)
Interferon	7 (4%)
DNMTi	11 (5%)
Other	39 (19%)
Allo-HSCT	6 (3%)
<b>MPN-AP/BP characteristics</b>	<b>N = 202</b>
Age at accelerated/blast phase MPN, median (range)	68.6 (22.7-94.0)
Latency period in years between chronic-phase MPN and MPN-AP/BP, median (range)	4.5 (0.0-44.2)
WBC (10 <sup>3</sup> /μL), median (range)	9.8 (0.6-144.6)
Hemoglobin (g/dL), median (range)	8.6 (5.1-16.5)
Platelets (10 <sup>3</sup> /μL), median (range)	99.0 (4.0-1839.0)
Peripheral blast %, median (range)	13.0 (0.0-91.0)
Marrow blast %, median (range)	22.0 (0.0-97.0)
Creatinine (g/dL), median (range)	0.95 (0.5-7.0)
Total bilirubin (g/dL), median (range)	0.7 (0.2-3.4)
Palpable splenomegaly, n (%)	102 (52.0)
<b>2017 ELN risk at MPN-AP/BP diagnosis</b>	<b>n = 189</b>
Favorable	5 (2.6)
Intermediate	58 (30.7)
High risk	126 (66.7)
<b>Mutations at MPN-AP/BP diagnosis</b>	<b>n = 166</b>
ASXL1	52 (31%)
TP53	43 (26%)
SRSF2	39 (23%)
IDH2	24 (14%)
EZH2	15 (9%)

**Table 1 (continued)**

Demographics	N = 202
U2AF1	12 (7%)
IDH1	11 (7%)

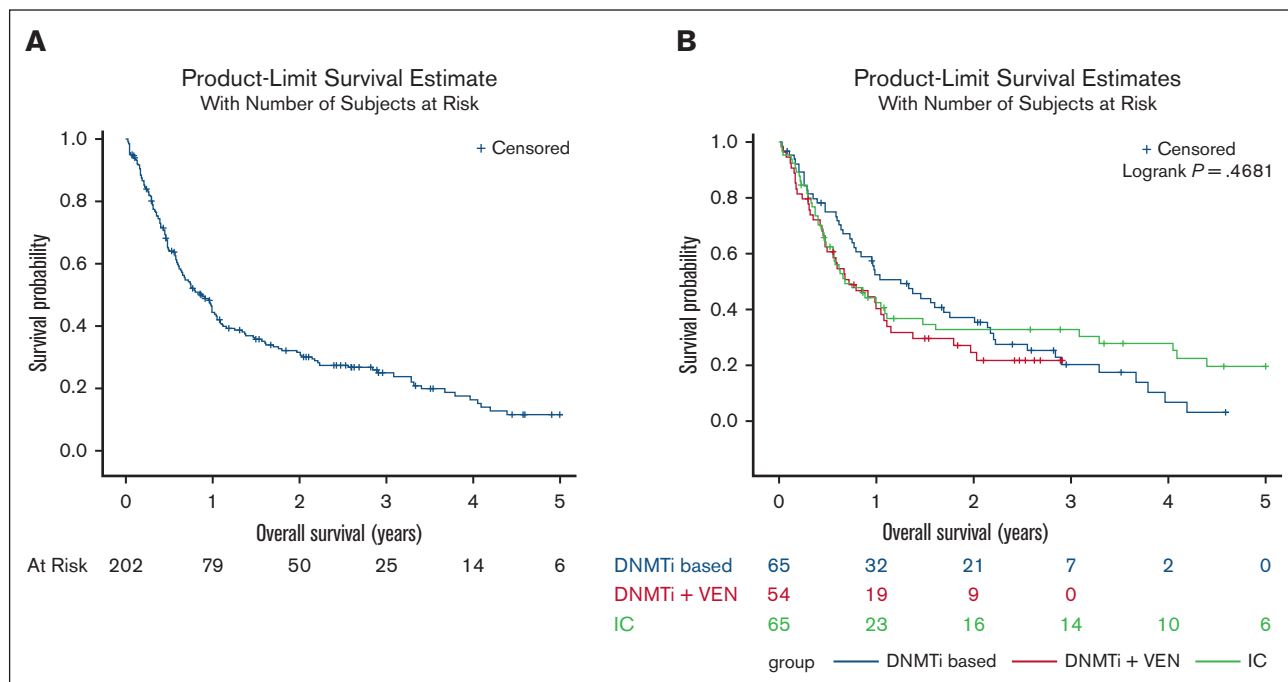
We also analyzed response to first-line treatment approach by both 2017 ELN and 2012 MPN-BP criteria, which is summarized in Table 3. The complete remission/complete remission with incomplete count recovery (CR/CRi) rate by 2017 ELN was 42% for the IC group, 41% for the DNMTi + VEN-based group, and 20% for the DNMTi-based group; when analyzing by 2012 MPN-BP response criteria the rate of acute leukemia response–complete (ALR-C) or better was 37% for the IC group, 39% for the DNMTi + VEN-based group, and 22% for the DNMTi-based group. Kaplan-Meier analysis of survival by 2017 ELN criteria demonstrated a median OS of 1.37 years for those that achieved a CR/CRi compared with 1.05 years for those that achieved partial remission (PR) or morphologic leukemia-free state (MLFS) and 0.59 years for those that achieved stable disease (SD) or treatment failure (TF;  $P = .0002$ ; Figure 2A). Analyzing OS by 2012 MPN-BP response demonstrated a median OS of 1.75 years for those that achieved ALR-C or better compared with 0.74 years for those that achieved acute leukemia response–partial and 0.61 years for those that achieved SD or progressive disease ( $P = .006$ ; Figure 2B).

A total of 115 therapies were used in the second-line and beyond (2L+) setting for MPN-AP/BP with only 18 administered in the context of a clinical trial. The specific therapies are summarized in supplemental Table 2 whereas the response to therapy is in Table 4.

In an effort to better understand factors affecting OS beyond treatment choice, we performed a univariate analysis of several clinical and molecular/cytogenetic factors at time of MPN-AP/BP diagnosis, summarized in Table 5. Stratification of age, hemoglobin, white blood count (WBC), and platelet count was derived from the Mutation-enhanced International Prognostic Score System–Plus, version 2.0, whereas stratification of blast percentage was derived from definitions of chronic-phase, accelerated-phase, and blast-phase MPN.<sup>4,30</sup> Stepwise Cox regression was performed to determine which factors from Table 5 were significant in a multivariate model (Table 6), and included age of >65 years (hazard ratio [HR], 1.87; 95% confidence interval [CI], 1.27-2.77), WBC of >25 × 10<sup>3</sup>/μL (HR, 2.35; 95% CI, 1.59-3.49), hemoglobin of >10 g/dL vs <8 g/dL (HR, 0.44; 95% CI, 0.27-0.72), hemoglobin of 8 to 10 g/dL vs < 8 g/dL (HR, 0.63; 95% CI, 0.43-0.93), and TP53 mutation (HR, 2.15; 95% CI, 1.46-3.15). The stepwise Cox model included a  $P$  value for entry of 0.50 and a  $P$  value to remain of 0.15 for the potential factors.

### Outcomes in patients that received allo-HSCT

Overall, 65 patients from our cohort went onto receive allo-HSCT for MPN-AP/BP. Characteristics of patients that underwent allo-HSCT are summarized in supplemental Table 3. One patient proceeded directly to allo-HSCT after MPN-AP/BP diagnosis, 44 patients proceeded after first-line therapy, and 20 patients proceeded to allo-HSCT after 2L+ therapies. Fifty-one patients had next-generation sequencing performed at time of MPN-AP/BP



**Figure 1. Overall survival of patients diagnosed with accelerated/blast-phase myeloproliferative neoplasms from 2017 onward.** (A) OS of patients diagnosed with MPN-AP/BP from 2017 onward. (B) OS of patients with MPN-AP/BP by frontline treatment approach.

diagnosis; nondriver mutations with an incidence of  $\geq 10\%$  were *ASXL1* (29%), *RUNX1* (24%), *TP53* (20%), *SRSF2* (20%), *TET2* (18%), *IDH1* (10%), and *IDH2* (10%). To better understand how disease characteristics and treatment choices may have affected receipt of allo-HSCT, we performed univariate analysis of the variables summarized in supplemental Table 4A at time of MPN-AP/BP diagnosis. Stepwise logistic regression using the predictors shown in supplemental Table 4A resulted in the following statistically significant factors for receipt of allo-HSCT: age of  $\geq 65$  years, WBC of  $>25 \times 10^3/\mu\text{L}$ , and hemoglobin of  $>10$  g/dL vs  $< 8$  g/dL (supplemental Table 4B). The stepwise logistic model included a *P* value for entry of 0.50 and a *P* value to remain of 0.15 for the potential factors.

Among 65 patients who received allo-HSCT, donor source was the following: 36 matched unrelated donors, 11 matched related donors, 11 haplo-identical donors, 6 mismatched unrelated donors, and 1 cord blood. Sixty patients received a reduced-intensity regimen whereas 15 patients received a myeloablative regimen. Twenty-five patients developed acute graft versus host disease whereas 16 developed chronic graft versus host disease. We analyzed survival outcomes using the Kaplan-Meier method. Median OS from the time of MPN-AP/BP diagnosis was 3.1 years and was 2.30 years from the time of allo-HSCT (Figure 3A-B). Thirty patients were alive at time of the data lock and among them 6 had relapsed MPN-AP/BP after allo-HSCT. Among 35 patients who died after allo-HSCT, the cause of death was noted as transplant related in 16, and relapse of MPN-AP/BP in 15 patients; 4 patients died of causes not related to allo-HSCT or MPN-AP/BP. The 2-year rate of relapse after allo-HSCT was 23% and 2-year nonrelapse-related mortality rate after allo-HSCT was 25%.

We also analyzed several factors to try and identify what may correlate with improved OS in patients after allo-HSCT. We

performed Kaplan-Meier analysis of OS from time of allo-HSCT based on 2017 ELN disease response going into allo-HSCT; median OS was 2.85 years in patients with CR/CRi, 2.30 years for those with PR or MLFS, and 0.74 years for those with SD or TF (*P* = .4994; Figure 3C). The median OS from time of allo-HSCT was significantly longer for those that achieved CR/CRi/PR/MLFS than for those that achieved SD/TF as best response before allo-HSCT (1.37 years vs 0.59 years, *P* < .0001). We also performed univariate analysis of the variables at time of MPN-AP/BP diagnosis, summarized in supplemental Table 5A, to identify potential factors associated with OS from time of allo-HSCT. Multivariate analysis identified age of  $\geq 65$  years, marrow blasts of 10% to 19% vs  $< 10\%$ , serum creatinine (g/dL), and *TP53* mutation status as being significant factors (supplemental Table 5B). The stepwise logistic model included a *P* value for entry of 0.50 and a *P* value to remain of 0.15 for the potential factors.

## Discussion

This series of 202 patients is, to our knowledge, the largest cohort of patients with MPN-AP/BP diagnosed and treated in the current era of myeloid therapies. Given the size of our cohort, heterogeneity in frontline treatment approaches, number of patients that proceeded to allo-HSCT, and response assessment using both AML and MPN-BP specific criteria, we were able to report on survival across a variety of dimensions. In addition, we were able to investigate the baseline factors that may influence frontline treatment choice and receipt of allo-HSCT.

The median OS in the entire cohort was 0.86 years, which is consistent with the survival reported in historical cohorts.<sup>8,9,31</sup> There was no significant difference in OS based on front-line treatment approach. Patients that received IC were significantly younger whereas those that received DNMTi-based therapy had

**Table 2. Characteristics of patients with MPN-AP/BP treated with intensive chemotherapy, DNMTi-based therapy, and DNMTi + VEN-based therapy**

Variable, mean (SD)	IC (n = 65)	DNMTi + VEN-based (n = 54)	DNMTi-based (n = 65)	P value
Age (y) at diagnosis of MPN-AP/BP	62.9 (8.6)	71.2 (7.4)	69.7 (10.5)	<.0001*
WBC (10 <sup>3</sup> /μL)	17.6 (21.5)	23.5 (26.4)	21.8 (33.1)	.48*
Platelet (10 <sup>3</sup> /μL)	188.7 (287.4)	184.4 (203.8)	235.5 (330.1)	.54*
Hemoglobin (g/dL)	9.3 (2.2)	8.9 (1.9)	8.8 (1.6)	.33*
Peripheral blasts (%)	24.5 (22.9)	21.0 (22.9)	13.5 (14.4)	.009*
Marrow blasts (%)	36.8 (22.1)	34.6 (23.9)	21.9 (19.0)	.0006*
Total bilirubin (g/dL)	0.8 (0.6)	0.8 (0.4)	0.9 (0.5)	.70*
Creatinine (g/dL)	1.0 (0.3)	1.2 (0.5)	1.0 (0.9)	.15*
Splenomegaly	30 (48.4)	21 (39.6)	39 (61.9)	.052
<b>Chronic-phase MPN</b>				
Polycythemia vera	14 (21.5)	9 (16.7)	14 (21.5)	.22
Essential thrombocythemia	22 (33.9)	15 (27.8)	17 (26.2)	
Primary myelofibrosis	13 (20.0)	18 (33.3)	26 (40.0)	
Other	16 (24.6)	12 (22.2)	8 (12.3)	
<b>Driver mutation</b>				
JAK2	37 (56.9)	38 (70.4)	39 (60.0)	.30
CALR	9 (13.9)	7 (13.0)	13 (20.0)	.50
MPL	8 (12.3)	6 (11.1)	5 (7.7)	.67
Triple-negative	13 (20.0)	4 (7.4)	10 (15.4)	.15
<b>Mutations</b>				
ASXL1	13 (20.0)	16 (29.6)	16 (24.6)	.48
EZH2	4 (6.2)	3 (5.6)	7 (10.8)	.61†
SRSF2	7 (10.8)	19 (35.2)	8 (12.3)	.0008
IDH1	3 (4.6)	3 (5.6)	4 (6.2)	1.00†
IDH2	7 (10.8)	6 (11.1)	6 (9.2)	.94
U2AF1	4 (6.2)	5 (9.3)	3 (4.6)	.66†
RUNX1	7 (10.8)	11 (20.4)	8 (12.3)	.28
TP53	11 (15.9)	13 (24.1)	14 (21.5)	.62

\*Analysis of variance F-test.

†Fisher exact test.

significantly lower marrow and peripheral blood blasts; these findings may help to elucidate some of the factors that underlie the selection of specific therapies. Interestingly, although CR rates were numerically higher with IC and DNMTi + VEN-based approaches, patients that received DNMTi-based approaches had numerically longer OS. Although comprehensive adverse event data were not collected, this may speak to the ability of patients to stay on DNMTi-based therapy with disease control even if a CR is not achieved.

Among the patients who received allo-HSCT in our cohort, the median OS was 2.3 years from time of allo-HSCT. The significant variables affecting receipt of allo-HSCT include age, WBC, hemoglobin, marrow blast percent, triple-negative disease status, and TP53 mutation status. When looking at disease control before allo-HSCT by 2017 ELN criteria, there was no significant association between response and OS after allo-HSCT. Of note, median OS was longer for patients that achieved CR/CRi/PR/MLFS before allo-HSCT than for those that had SD/TF. This suggests

that reduction in blast burden may be of some benefit but the necessity of achieving CR/CRi is not clear. The allo-HSCT survival data reported in our cohort are consistent with previously reported data demonstrating that allo-HSCT seems to offer durable OS in patients with MPN-AP/BP<sup>32,33</sup> but that the majority of patients do not receive allo-HSCT.<sup>9</sup> Potential reasons for a minority of patients with MPN-AP/BP receiving allo-HSCT may be the relative lack of CRs achieved with current therapeutic options, age at diagnosis of disease, and defining pretransplant disease control using AML-specific criteria.

There is also significant discussion in the literature about the best way to gauge response in patients with MPN-AP/BP. When comparing outcomes of MPN-BP in remission at time of allo-HSCT compared with both de novo AML and AML arising from MDS, median OS is significantly shorter and the risk of relapse is significantly higher.<sup>34</sup> This serves to highlight that typical AML response criteria may not appropriately capture the depth of response to therapy among patients with MPN-AP/BP. This

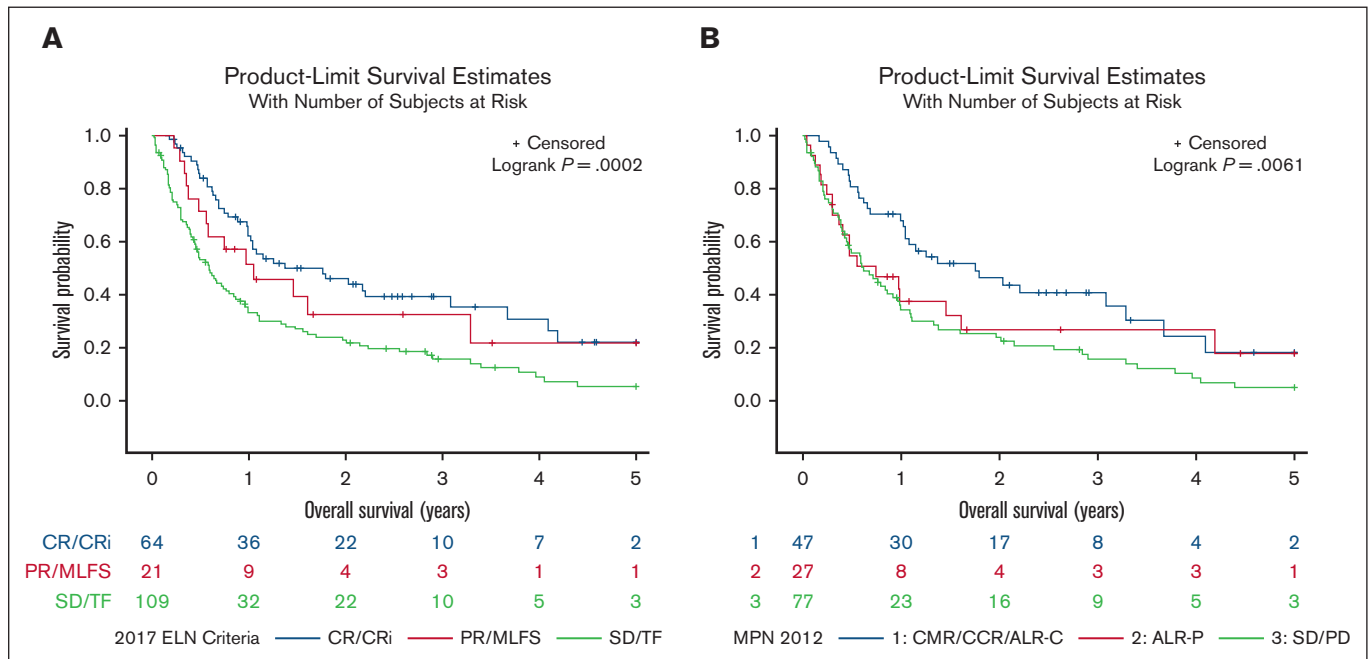
**Table 3. Response to first-line therapies for MPN-AP/BP**

Therapy	2017 ELN response	2012 MPN-BP response
<b>IC (n = 65)</b> (n = 65 evaluable for ELN) (n = 51 evaluable for MPN-BP)	CR: 28% CRi: 14% MLFS: 2% PR: 11% TF: 45%	CCR: 8% ALR-C: 29% ALR-P: 20% SD: 10% PD: 17%
<b>DNMTi + VEN based (n = 54)</b> (n = 54 evaluable for ELN) (n = 42 evaluable for MPN-BP)	CR: 22% CRi: 19% MLFS: 6% PR: 4% SD: 17% TF: 32%	CCR: 2% ALR-C: 37% ALR-P: 20% SD: 15% PD: 27%
<b>DNMTi based (n = 65)</b> (n = 65 evaluable for ELN) (n = 49 evaluable for MPN-BP)	CR: 9% CRi: 11% MLFS: 2% PR: 9% SD: 32% TF: 37%	CMR: 6% CCR: 2% ALR-C: 14% ALR-P: 12% SD: 37% PD: 33%
<b>Targeted monotherapy (n = 4)</b> (n = 4 evaluable for ELN) (n = 4 evaluable for MPN-BP)	CRi: 25% SD: 50% TF: 25%	ALR-P: 50% SD: 50%
<b>Other therapies (n = 6)</b> (n = 6 evaluable for ELN) (n = 6 evaluable for MPN-BP)	CRi: 17% PR: 17% SD: 17% TF: 30%	ALR-C: 17% ALR-P: 17% SD: 33% PD: 33%

ALR-P, acute leukemia response–partial; CCR, complete cytogenetic response; CMR, complete molecular response; PD, progressive disease; PR, partial remission.

observation may be because of the fact that even when therapies eradicate the AP/BP component of disease, features of the chronic phase MPN often persist, such as marrow fibrosis and circulating peripheral blasts. The 2012 MPN BP criteria<sup>29</sup> were designed with

these limitations in mind, but use of these criteria has not been widely adopted in studies focused on MPN-AP/BP. Our analysis of 2017 ELN response criteria demonstrated that achievement of CR/CRi was associated with longer OS when compared with other



**Figure 2. Overall survival of patients with MPN-AP/BP stratified by response.** (A) OS of patients with MPN-AP/BP by 2017 ELN response criteria. (B) OS of patients with MPN-AP/BP by 2012 MPN-BP criteria. ALR-P, acute leukemia response–partial; CCR, complete cytogenetic response; CMR, complete molecular response; PD, progressive disease; PR, partial remission.

**Table 4. Response to second-line and beyond therapies for MPN-AP/BP**

Therapy	2017 ELN response	2012 MPN-BP response
<b>DNMTi + VEN based (n = 38)</b>	CR: 5%	CCR: 3%
(n = 38 evaluable for ELN)	CRi: 5%	ALR-C: 22%
(n = 36 evaluable for MPN-BP)	MLFS: 16%	ALR-P: 14%
	PR: 5%	SD: 22%
	SD: 13%	PD: 39%
	TF: 55%	
<b>IC (n = 37)</b>	CR: 16%	CCR: 6%
(n = 37 evaluable for ELN)	CRi: 3%	ALR-C: 15%
(n = 34 evaluable for MPN-BP)	MLFS: 14%	ALR-P: 29%
	PR: 11%	SD: 21%
	SD: 19%	PD: 29%
	TF: 38%	
<b>DNMTi based (n = 16)</b>	CR: 6%	ALR-C: 14%
(n = 16 evaluable for ELN)	MLFS: 6%	ALR-P: 21%
(n = 14 evaluable for MPN-BP)	PR: 6%	SD: 29%
	SD: 25%	PD: 36%
	TF: 56%	
<b>Targeted monotherapy (n = 11)</b>	CR: 9%	CCR: 10%
(n = 11 evaluable for ELN)	CRi: 18%	ALR-C: 30%
(n = 10 evaluable for MPN-BP)	MLFS: 18%	ALR-P: 20%
	SD: 18%	SD: 20%
	TF: 36%	PD: 20%
<b>Other therapies (n = 13)</b>	CR: 8%	ALR-C: 15%
(n = 13 evaluable for ELN)	CRi: 8%	ALR-P: 31%
(n = 13 evaluable for MPN-BP)	PR: 23%	SD: 31%
	SD: 38%	PD: 23%
	TF: 23%	

Abbreviations are explained in Table 3.

responses; similar findings were seen in patients that achieved an ALR-C or better by MPN-BP 2012 criteria. Median OS was 1.37 years in patients that achieved CR/CRi by 2017 ELN criteria whereas median OS was 1.75 years in those who achieved ALR-C or better by 2012 MPN-BP criteria. These data suggest that use of 2012 MPN-BP criteria when assessing therapeutic response may be as useful, and perhaps more relevant in this population, as the 2017 ELN AML-specific criteria. It remains to be determined how to best characterize disease control before allo-HSCT.

Lastly, our analysis sought to characterize the frequency of clinical trial enrollment in our cohort. Only 14% of patients in our cohort were treated in the context of a clinical trial for their frontline therapy; only 12% of 2L+ therapies were administered via clinical trial. Novel therapies are desperately needed for this patient group. An ongoing prospective trial investigating combined IDH2/JAK2 inhibition has noted promising preliminary results.<sup>35</sup> In addition, preclinical work has identified other potential therapeutic targets including hypoxia-inducible factor and DUSP6; in addition, there may be a role for bromodomain and extra-terminal domain inhibition, lysine specific demethylase 1 inhibition, B-cell lymphoma-extra large, and cyclin-dependent kinase 9 inhibition in MPN-AP/BP as well.<sup>36-41</sup>

Our study has limitations given its retrospective nature. Although this was a multicenter study, the centers included may not fully represent the breadth of patients with MPN-AP/BP. We were also unable to assess for both 2017 ELN response criteria and 2012 MPN-BP criteria in the entire cohort. In addition, there may be factors influencing treatment approach and receipt of allo-HSCT that were not adequately captured.

**Table 5. Univariate analysis of factors affecting OS in MPN-AP/BP**

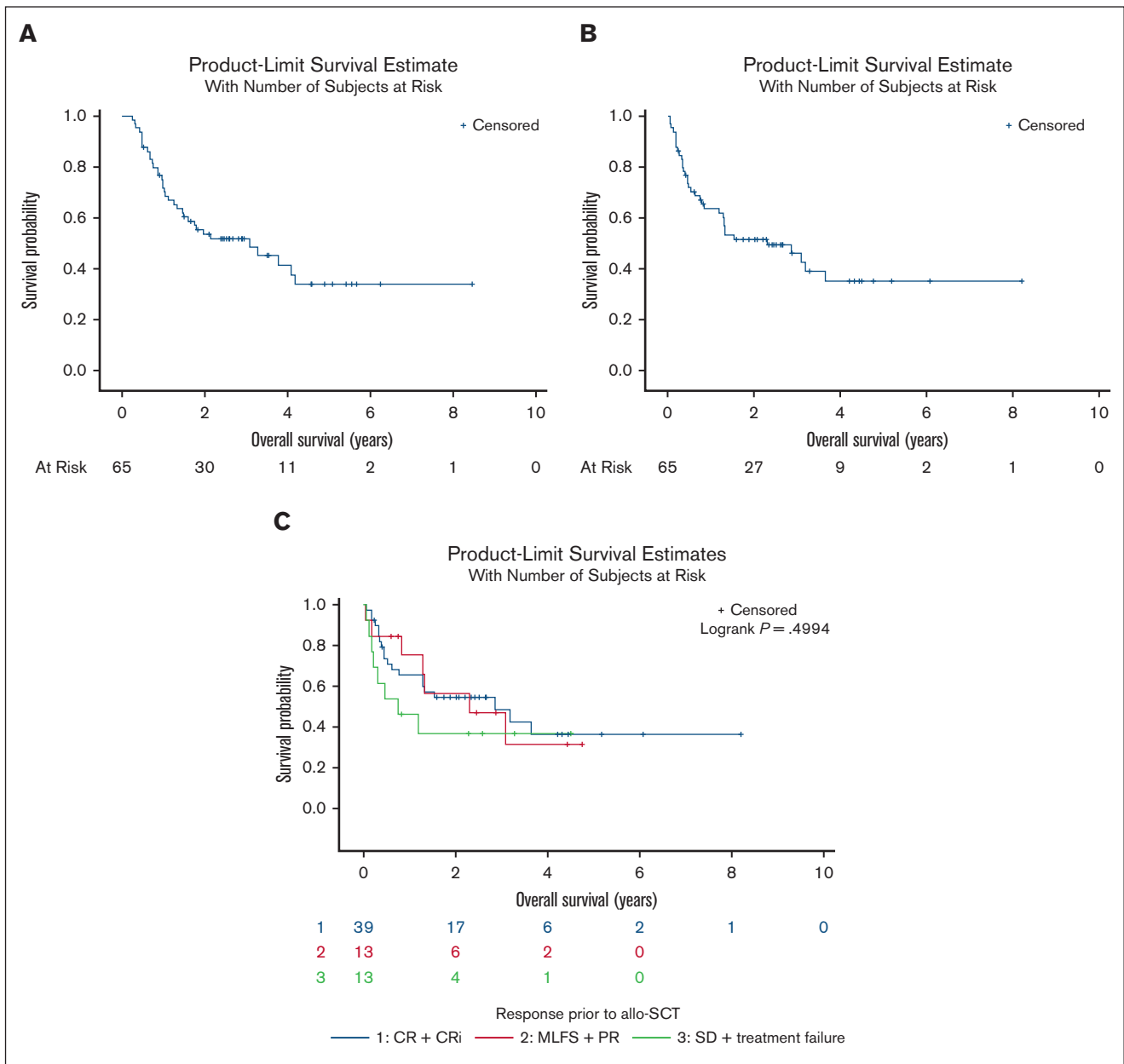
Variable	HR (95% CI)	P value
Age ≥ 65 y	1.840 (1.271, 2.667)	.001
WBC > 25 × 10 <sup>3</sup> /μL	1.812 (1.267, 2.590)	.001
Platelet > 100 × 10 <sup>3</sup> /μL	0.687 (0.497, 0.947)	.022
Hemoglobin > 10 g/dL vs < 8 g/dL	0.380 (0.240, 0.603)	<.0001
Hemoglobin 8-10 g/dL vs < 8g/dL	0.626 (0.436, 0.899)	.011
Peripheral blasts ≥ 20% vs < 10%	1.414 (0.956, 2.094)	.08
Peripheral blasts 10%-19% vs < 10%	1.242 (0.826, 1.867)	.30
Marrow blasts ≥ 20% vs <10%	0.882 (0.456, 1.703)	.71
Marrow blasts 10%-19% vs <10%	0.805 (0.399, 1.626)	.55
Total bilirubin	0.896 (0.647, 1.242)	.51
Creatinine	1.164 (0.903, 1.502)	.24
Splenomegaly	1.259 (0.908, 1.746)	.17
<b>Driver mutation status</b>		
JAK2	0.970 (0.697, 1.351)	.86
CALR	1.056 (0.690, 1.617)	.80
MPL	1.848 (1.078, 3.166)	.03
Triple negative	0.722 (0.436, 1.197)	.21
<b>2017 ELN risk</b>		
High risk vs intermediate/favorable	1.859 (1.282, 2.696)	.001
<b>Mutation status</b>		
TP53	2.085 (1.456, 2.996)	<.0001
IDH1	0.885 (0.433, 1.808)	.74
IDH2	0.664 (0.389, 1.134)	.13
ASXL1	0.897 (0.616, 1.307)	.57
EZH2	1.076 (0.609, 1.901)	.80
SRSF2	1.113 (0.742, 1.671)	.60
RUNX1	0.774 (0.483, 1.241)	.29
<b>Chronic-phase MPN type</b>		
ET vs other	1.134 (0.694, 1.853)	.62
PMF vs other	1.194 (0.737, 1.935)	.47
PV vs other	1.352 (0.803, 2.278)	.26

ET, essential thrombocythemia; PMF, primary myelofibrosis; PV, polycythemia vera.

In summary, our study demonstrates that, even with new therapeutic approaches available for MPN-AP/BP, OS is quite limited. Only a minority of patients are treated in the context of a clinical trial, thus highlighting a significant need to not only develop novel and effective therapies but to also evaluate them in clinical trials inclusive of patients with MPN-AP/BP. Furthermore, prospective

**Table 6. Multivariate analysis of factors affecting OS in MPN-AP/BP**

Variable	HR (95% CI)	P value
Age ≥ 65 y	1.870 (1.265, 2.765)	.002
WBC > 25 × 10 <sup>9</sup> /L	2.354 (1.589, 3.488)	<.0001
Platelet > 100 × 10 <sup>9</sup> /L	0.443 (0.272, 0.723)	.001
Hemoglobin > 10 g/dL vs < 8 g/dL	0.629 (0.425, 0.929)	.02
TP53 mutation status	2.146 (1.460, 3.153)	.0001
Splenomegaly	1.305 (0.925, 1.842)	.13



**Figure 3. Overall survival of patients with MPN-AP/BP that underwent allogeneic hematopoietic stem cell transplantation.** (A) OS of patients with MPN-AP/BP that underwent allo-HSCT from time of diagnosis. (B) OS from time of allo-HSCT in patients with MPN-AP/BP. (C) OS from time of allo-HSCT in patients with MPN-AP/BP stratified by 2017 ELN response before allo-HSCT. PD, progressive disease.

evaluation of both 2017 ELN and 2012 MPN-BP response criteria as well as other recently proposed MPN-AP/BP criteria is needed to ascertain the best method of response assessment.<sup>42</sup>

## Authorship

Contribution: A.A.P. designed the study plan, performed data analysis, and wrote the manuscript; J.J.Y. offered input into the study plan, collected data, and reviewed/revised the manuscript; J.F.C. performed data analysis and reviewed/revised the manuscript; O.O. designed the study plan and reviewed/revised the

manuscript; and all other authors collected data and reviewed/revised the manuscript.

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